Citation:

Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006; 354 (15): 1,578-1,588

PubMed ID: 16531614

Study Design:

Randomized controlled trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine the efficacy of homocysteine-loweringtreatment with B vitamins for secondary prevention in patientswho had had an acute myocardial infarction (MI).

Inclusion Criteria:

Men and women 30 to 85 years of age who had had an acute MI within seven days before randomization were eligible to participate.

Exclusion Criteria:

- Presence of coexisting disease associated with a life expectancy of less than four years
- Prescribed treatment with B vitamins
- Untreated vitamin B deficiency
- Inability to follow the protocol, as judged by the investigator.

Description of Study Protocol:

Recruitment

Unclear.

Design

RCT, multi-center, prospective, double-blind, 2x2 factorial design.

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Blinding Used

Double blind.

Intervention

- Four groups:
  - Group 1: Combination group: 0.8mg of folic acid, 0.4mg of vitamin B_{12}, and 40mg of vitamin B_6 per day
  - Group 2: 0.8mg of folic acid plus 0.4mg of vitamin B_{12} per day
  - Group 3: 40mg of vitamin B_6 per day
  - Group 4: Placebo
- Study medication was given in a single capsule, taken once per day. For the first two weeks after enrollment, the combination-therapy group and the group given folic acid and vitamin B_{12} received a loading dose of 5mg of folic acid per day, whereas the other two groups received placebo for the first two weeks. Capsule formulations were manufactured (Alpharma) to be indistinguishable by color, weight or their ability to dissolve in water
- Participants were given standard post–MI therapy and were seen at a follow-up visit at two months and at a final visit after 2.0 to 3.5 years
- Every six months after enrollment, study medication and a questionnaire were mailed to the participants. They were asked about study outcomes, compliance and adverse effects. Those who did not return the questionnaire were interviewed by telephone by study personnel or records were consulted to determine their vital status. Staff members at the coordinating center visited all participating hospitals to monitor data quality
- Smerud Medical Research, on behalf of the Norwegian Research Council, conducted an audit of the trial and approved it
- Blood samples were obtained from all available participants at baseline, at two months and at the final visit for the measurement of plasma total homocysteine, serum folate and serum cobalamin. Levels of these vitamins were determined with the use of published methods.

Statistical Analysis

- Sample size calculation was based on data from previous Scandinavian trials, assuming the three-year rate of the primary end point would be 25 percent in the placebo group
- The planned enrollment of 3,500 patients, with an average follow-up of 3.0 years, was expected to result in 750 primary events and give the study a statistical power of more than 90 percent to detect a 20 percent relative reduction in the rate of the primary end-point, given a two-sided alpha value of 0.05

- All analyses were conducted according to the intention-to-treat principle. The main focus was on comparison of treatment with folic acid and vitamin B_{12} with control (the combination-therapy group and the group given folic acid and vitamin B_{12} vs. the vitamin B_6 and placebo groups) and comparison of treatment with vitamin B_6 with control (the combination-therapy group and the group given vitamin B_6 vs. the group given folic acid and vitamin B_{12} and the placebo group). The factorial design also allowed a comparison of the combination-therapy group with the placebo group
- Estimates of the hazard ratios and 95 percent confidence intervals were obtained with the use of Cox proportional-hazards models
- Interactions were identified by applying the likelihood ratio test to models with the interaction term and those without the interaction term and comparing the result
- Kaplan–Meier survival analysis was used to compare the cumulative incidence of the primary end-point in the four groups
- Differences between groups in baseline characteristics were tested with analysis of variance. Study center was included as a covariate in all analyses
- The reported P-values are two-sided and are not adjusted for multiple comparisons.

Data Collection Summary:

Timing of Measurements

Baseline, follow-up at two months and at a final visit between 2.5-3.0 after baseline measurements.

Dependent Variables

Primary end-point:

- Composite of new non-fatal and fatal MI, non-fatal and fatal stroke and sudden death attributed to CHD
- Patients who were resuscitated after cardiac arrest were included in the analysis of the primary end-point, whereas those with a silent MI were not
- For each participant, only the first of all such events was included in the analysis of the primary end-point. If death occurred within 28 days after the onset of an event, the event was classified as fatal

Secondary end-points:

- Myocardial infarction, unstable angina pectoris requiring hospitalization, coronary revascularization with percutaneous coronary intervention or coronary-artery bypass grafting, stroke and death from any cause
- Incident cases of cancer were recorded as a measure of safety
- Acute coronary events were categorized according to symptoms, new changes on electrocardiography and levels of cardiac biomarkers
- An unequivocal global or focal neurologic deficit that occurred suddenly and lasted more than 24 hours was required for the diagnosis of stroke
- Blood samples for plasma total homocysteine, serum folate and serum cobalamin.

Independent Variables

Treatment group assignment.

Control Variables

- The baseline level of total homocysteine was a significant predictor of the primary end-point (RR associated with a 3-µmol difference in the total homocysteine level, 1.05; 95 percent confidence interval, 1.01 to 1.09; P=0.01) after adjustment for study center, age, sex, systolic blood pressure, total cholesterol level and smoking status
- After additional adjustment for the creatinine level, the RR was 1.03 (P=0.10).

Description of Actual Data Sample:

- *Initial N:* 3,749
- *Attrition:* Five withdrew after informed consent and did not receive assigned treatment, 404 (11%) stopped taking study medication during the trial but this was not different across groups
- *Age:* Mean age 63.6±11.9, 63.2±11.6, 62.5±11.7, 32.6±11.4 (P=0.11) for combination group, folic acid plus B_{12}, B_6 and the placebo group, respectively
- *Ethnicity*: Unclear
- *Other relevant demographics:* Group differences for "current smoker" and "warfarin"
- *Anthropometrics:* Yes
- *Location*: 35 Norwegian hospitals.

	Folic Acid, B_{12} and B_6 (N=937)	Foli Acid and B_{12} (N=935)	B_6 (N=934)	Placebo (N=943)	P-value
Age (year)	63.6±1.9	63.2±11.6	62.5±11.7	62.6±11.4	0.11
Male sex (percent)	684±(73)	696 (74)	686 (73)	705 (75)	0.80
BMI	26.5±4.0	26.2±3.5	26.3±3.8	26.3±3.8	0.66

Summary of Results:

- Mean follow-up was 36 months, compliance was between 93-99% and did not differ significantly between treatment groups
- Among those who received folic acid, the mean total homocysteine level was a mean of 4.2µmol per liter (0.57mg per liter) lower than the level in the group that did not receive folic acid after two months (a difference of 31%, P<0.001) and 3.8µmol per liter (0.51mg per liter) lower at the end of the intervention (a difference of 28%, P<0.001). The mean total homocysteine level did not change significantly in the group treated with vitamin B_6 alone.

Treatment with folic acid and vitamin B_{12} led to significant increases, by a factor of five to six, in the mean levels of plasma folate and increases in plasma vitamin B_{12} by approximately 60 percent
- Treatment with folic acid in combination with vitamin B_{12}, with or without vitamin B_6, did not significantly reduce the risk of the primary end-point, as compared with placebo. Both treatment regimens were associated with a non-significant increase in risk, mainly driven by an event rate that was 22% higher in the combination-therapy group than in the placebo group (P=0.05)
- The cumulative hazard ratio for the combination-therapy group, as compared with the other three groups, was 1.20 (95% CI, 1.02 to 1.41; P=0.03). The result remained the same after adjusting for the use of warfarin at baseline, which differed among the four groups
- The risk of the secondary end-points was not significantly influenced by treatment with folic acid and vitamin B_{12}. Vitamin B_6 therapy was associated with a 17% increase in the risk of MI (P=0.05) and combination therapy was associated with a 30% increase in the risk of nonfatal MI (P=0.05)
- Sub-group analyses of the primary end-point indicated that treatment with B vitamins was not associated with a significant benefit in any sub-group. An increased risk associated with treatment was observed among patients with higher baseline levels of total homocysteine (more than 13µmol per liter, vs. 13µmol per liter or less) who received combination therapy (P=0.04) and among those with an MI without ST-segment elevation who received folic acid and vitamin B_{12} (P=0.04).

Author Conclusion:

The NORVIT trial demonstrated that intervention with folic acid, with or without high doses of vitamin B_6, did not lower the risk of recurrent cardiovascular disease or death after an acute MI. Such therapy may even be harmful after acute MI or coronary stenting and should therefore not be recommended.

Reviewer Comments:

- *Although there was no significant difference between groups for the secondary end-point, the author's noted that the analyses were not adjusted for multiple comparisons and that apparent associations could readily be explained by chance*
- *Author's stated that non-compliance is not a likely explanation for the negative findings*
- *Power of the trial was slightly less than planned.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	No
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	Yes
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes

10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes